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An overview of challenges to eradication of *Helicobacter pylori* infection and future prospects

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Abstract. – The eradication of *H. pylori* infection continues to be a challenge due to the evolution of drug-resistant bacteria, lack of a gold standard diagnostic method, and ineffectiveness of current vaccines. Additionally, there still is no consensus in the literature about the main source of gastric *H. pylori* infection. The bacterium has also been demonstrated to colonize in dental plaque and the oral cavity. We believe that to develop new approaches for successful eradication of the disease, factors such as the biology of the bacterium, reservoir differentiations, host-bacterium interactions and problems in diagnosis, treatment and vaccination must be comprehensively considered.

Therefore, the main goal of this study is to gather all of the literature analysis about the problems in the eradication of the infection, reconsider contradictions about extra-gastric reservoirs of the bacterium, and propose new strategies aimed at disease eradication.

Key Words
H. pylori, Infection, Eradication, Diagnosis, Vaccination, Dental plaque, Oral cavity.

Biology of *Helicobacter pylori* and Global Distribution

Helicobacter pylori (H. pylori) was first identified in 1982 by Marshall and Warren. It is a spiral or comma shaped, 0.6 x 3.5 micron sized, highly motile and slowly growing Gram-negative bacilli that colonizes in the antrum and cardia of the stomach of human and some primates, as well as in the gastric corpus and duodenum with gastric cell metaplasia[1-3]. As microaerophilic bacteria, *H. pylori* can only live in a <1% oxygen-containing environment. *H. pylori* includes a hydrogenase enzyme that is capable of producing energy via oxidation of the molecular hydrogen (H_2) produced by intestinal bacteria. The bacterium also contains catalase, oxidase and urease enzymes. The survival of *H. pylori* in the stomach without being affected by gastric acid is a result of urease activity. The bacteria produce ammonia and carbondioxyde while hydrolyzing urea. While ammonia integrates with H_2O to produce ammonium, it alkalizes the media by obtaining H ions and protects the bacteria from the harmful effects of gastric acid. The spiral shape and flagellates of *H. pylori* help the bacteria in crossing the mucus layer. Bacteria attaches to the gastric surface epithelium by adhesins, disintegrates the mucus with protease, potentiates the reverse diffusion, and mitigates the harmful effects of H ions by damaging the phospholipid rich surface epithel layer by lipase[4-8]. The bacteria colonize between mucus and epithelial cells and causes inflammation without invading gastric mucosa[7]. *H. pylori* infection is accepted as the most important chronic bacterial infection and the most significant factor of chronic gastritis. Additionally, the infection leads to other serious complications such as peptic ulcer (in 15-20% of *H. pylori* infected patients), complicated ulcer (2-12%), gastric cancer (1-3%), and primary gastric lymphoma (0.1%)[9-11]. There is also a relationship between non-Hodgkin's lymphoma of gastric mucosa-associated lymphoid tissue and *H. pylori* infection, although the evidence is weaker[12,13]. There are also some extradigestive and dermatologic manifestations of *H. pylori* infection such as chronic urticaria[14]. It is commonly accepted that almost half of the world is infected with H. pylori and the frequency of infection increases with age. In developed countries like the United States and some Western societies, the reported

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frequency of infection is 0-5% in children, 10-20% for those in their twenties, and increases to 30-50% in adults[15]. In comparison, *H. pylori* infection is more frequently seen in developing and non-developed countries. For instance, 80% of children in Western Africa are predicted to be infected with *H. pylori* before five years old. Insufficient socioeconomic conditions, poor hygiene, non-hygienic drinking water and preparation of nutrients in unsanitary conditions are responsible for almost 60-70% incidence of infection in children 5-10 years-old, and increases to 85-90% in adults[16-20].

Virulence Factors

H. pylori exerts its virulence on the colonized gastric mucosal cells in three sequential steps. The first step is adhesion and colonization on the gastric epithelial cell surface. The second step is evasion and attenuation of host defenses, and the last step is invasion and damage of the gastric mucosa[21,22]. Virulence factors of *H. pylori* take place in each of these pathogenic steps during infection. Adherence and colonization of the bacteria on gastric epithelial cells is the initial and crucial step of *H. pylori* infection. The release of urease from *H. pylori* protects the bacterium from gastric acidity and adapts the bacterium to the mucus layer[23,24]. Urease interacts with host HLA cell II molecules on gastric epithelial cells and enhanced expression of HLA II plays an active role in the stimulation of the apoptosis of epithelial cells[25-27]. Blood group antigen binding adhesin (BabA) is another virulence factor that binds to H-1 blood group antigens on normal gastric epithelial cells and also to major mucus components such as MUC5AC and MUC1 in the gastric mucus[28,29]. BabA induces interleukin-8 (IL-8) secretion and granulocytic infiltration that results in inflammation of the mucosa. Sialic acid-binding adhesin (SabA) is one of the key adhesins that binds to sialyl Lewis a and Lewis x antigens on inflamed gastric mucosal cells and adapts *H. pylori* to the dynamic conditions of the human stomach[30]. *H. pylori* virulence factors that take place in the immune invasion and attenuation step of infection are peptidoglycan (PGN), lipopolysaccharide (LPS), flagellins (FlaA and FlaB), superoxide dismutase (SOD) and catalase (KatA). LPS is a gram-negative bacterial endotoxin that targets some receptors in the TLR family on the gastric epithelial cell surface[31-34]. It inhibits macrophage activity and exerts an important role in immune escape, ensuring persistent bacterial colonization like PGN[34]. FlaA and FlaB evade the TLR5-mediated immune response of the host and facilitate *H. pylori* motility in gastric mucosa[35]. SOD is an antioxidant enzyme that counteracts the effects of oxidative stress by catalyzing the dismutation of superoxide to H_2O_2, which is subsequently converted into H_2O and O_2 by KatA. Additionally, the bacteria can easily maintain its persistence within gastric host cells[36]. The last step where *H. pylori* exerts its virulence is thru mucosal invasion and damage. CagA and VacA are two well-characterized virulence factors that generate detrimental intracellular signals. CagA is a translocated effector protein that modulates some signaling cascades involved in altering cell polarity, cell proliferation, pro-inflammatory response, interruption of cell-to-cell junctions and suppression of apoptosis and cell cycle[37,38]. VacA is another translocated effector protein that induces cellular injury by cell vacuolization, disruption of endosomal and lysosomal functions, membrane anion-selective channel formation, mitochondria-dependent apoptosis and immunomodulation[38-40].

Transmission of *H. pylori*

Transmission of the bacterium can occur thru two different modes: vertical or horizontal. In vertical transmission, H. pylori infection transmits from parents to children, while in horizontal transmission, people are infected with the bacterium via environmental contamination or social interactions[22,41]. Oral-oral transmission is possible across individuals by infected saliva containing H. pylori. Oral-oral transmission is supported by evidence obtained from transmission of bacteria by African mothers who chew nutrients before they feed their babies and by gnotobiotic beagle puppies infected by Helicobacter felis that transmit bacteria by licking uninfected animals[42,43]. One of the most common transmission routes of the bacterium is the fecal-oral route. *H. pylori* was successfully cultured by using stool samples of children from different regions of the world such as Gambia[44], England[45] and United States of America[46]. However, successful culture of bacteria is not always achieved due to rich bacterial flora in stool and this situation aggravates the toxic effects of stool over *H. pylori* [47-50]. Fecal-oral transmission has been verified indirectly from the results of South American studies. These studies[51-53] showed that water supplies that may contain *H. pylori* and

consumption of raw vegetables contaminated by human feces are significant risk factors for *H. pylori* infection. The role of flies as a vector of enteric illnesses has also been known for years. *H. pylori* has been isolated in houseflies, suggesting the possible role of houseflies in the fecal-oral transmission of bacteria[54]. Although very rare, human-to-human transmission by an iatrogenic route such as inadequately sterilized endoscopes is possible. Transmission by kissing or sexual relationship has been previously suggested; however, this has failed to be proven by studies. *H. pylori* infection is observed in domestic animals, but the frequency of infection is not increased in the owners of these pets. Hence, *H. pylori* infection is not accepted as a zoonotic infection[55,56]. Vomiting is a common condition in early childhood. In this situation, the transmission will be via gastric juice. Inhalation of gastric juice results in transmission of *H. pylori* and the bacteria may survive out of the stomach, which is not its typical environment. The gastro-oral route is an important transmission mode particularly in unhygienic environments. Moreover, in recent studies, *H. pylori* was detected at the tongue dorsum and the periodontal pockets with a nested PCR method. There was a significant relationship between tongue and fingernail positivity. According to these results, some researchers propose that *H. pylori* may be carried by hands and finger-mouth contact could be an important method of *H. pylori* transmission[57].

Diagnosis

Detection of *H. pylori*-associated infection is difficult since the infection can develop clinically silent or with non-specific symptoms. Gastroesophageal reflux, esophagitis, delayed gastric emptying, and various motility disorders can be accepted as signs of gastric *H. pylori* infection. However, these symptoms may also be observed in various childhood illnesses. Additionally, complaints of younger children are often unclear and not understandable when compared with older children and this makes the diagnosis of the infection more difficult for younger children[58-62]. Different tests are currently being applied in the diagnosis of *H. pylori* infection. Histopathological determination of gastrointestinal endoscopy or gastric biopsy is the most commonly performed invasive test and is particularly sensitive for revealing peptic ulcers[63]. However, expert pathologists are required for an accurate examination of the samples. Rapid Urease Test (RUT) is a diagnostic method that is used on biopsy specimens with a sensitivity of more than 90%. Its principle relies on degradation of urea into ammonia by the presence *H. pylori*, which is found in biopsy specimens and by the changes in environmental pH. Conversely, this method may reveal negative results in cases of active bleeding ulcers and intestinal metaplasia and in patients treated with proton pump inhibitors. This method may also give false-positive results when urease positive bacteria are present in the specimen[64-66]. Cultivation of *H. pylori* from gastric biopsies is another invasive technique and also the most specific. However, *H. pylori* culture requires specific agar and special atmospheric conditions that hinder its routine use in laboratories as a diagnostic method[67]. All these invasive methods have disadvantages due to difficulty in application and a negative impact on patient comfort. Because of these reasons, non-invasive methods are commonly applied[68]. The 13 C-Urea Breath Test is one of the oldest diagnostic techniques for *H. pylori* infection. The main principle of the 13 C-Urea breath test is oral administration of labeled urea, then its hydrolyzation by *H. pylori* bacteria in the stomach forms isotopically-labeled CO_2 that diffuses into the blood. Subsequent excretion of labeled CO_2 molecules is detected by testing equipment. Since *H. pylori* is the only pathogenic bacteria that evades gastric mucosa and also contains urease enzyme to breakup urea, the detection of labeled CO_2 within the breath of an individual following hydrolyzation of urea is a possible indicator for the presence of an *H. pylori* infection. Although the 13 C-urea Breath Test shows high sensitivity for adults, its sensitivity is lower for children and patients at the beginning of the disease. Additionally, it requires the use of gas chromatography and mass spectroscopy, which results in increased cost[69,70]. Serological tests can also be applied for the detection of the bacterium. Evaluation of IgG and IgM levels has good specificity, but moderate sensitivity (spec-78%, sen-69%). This situation is correlated with sighting of active disease in adults, but not in children. This method is not suitable for detecting the presence of the bacterium after treatment since serum antibodies can remain in the blood stream for a long time[71]. Stool tests that provide an opportunity to detect the bacterium in feces can also be used for diagnosis. Despite positive results, its accuracy varies due to the use of antibiotics and proton pump inhibitors[68]. Finally, PCR is another non-invasive technique that demonstrates the presence of the urease gene.

The main disadvantage of the PCR technique is its lower sensitivity value when few bacteria exist in specimens. Overall, as mentioned, there are many invasive and non-invasive techniques used for detection of *H. pylori*, but none of them are currently accepted as a gold standard. This situation presents an important problem and may decrease the success of treatment regimens. Therefore, continued research is necessary to further the development of new diagnostic techniques. In our recent work, we investigated the performance of the Micro Culture Method (MCM) on isolation and diagnosis of *H. pylori* in biopsy samples obtained from antrum and corpus of patients[72]. Previously, we observed that the MCM method is very successful in detecting *Leishmania* parasites independently of the number of the parasites[73,74]. It is known that MCM provides appropriate conditions such as O_2, CO_2 levels and pH for the growth of microaerophilic *Leishmania* parasites and microorganisms can easily proliferate in these conditions even if there are very low amounts of parasite in the sample. Hence, MCM provides an opportunity for easy, rapid and sensitive detection of *Leishmania*. According to our findings, MCM was found to be more sensitive and specific for diagnosis of Cutaneous and Visceral Leishmaniasis in contrast to conventional methods and it is now still being used for the purpose of diagnosis in different endemic regions of the world. Exactly like *Leishmania* parasite, *H. pylori* bacterium is a microaerophilic microorganism and requires similar conditions for their proliferation. Therefore, we proposed that MCM could also be used for detection of *H. pylori*. We found that MCM had an approximate 96% sensitivity, while the sensitivity of classical culture was 54%[74]. This data suggests that MCM has great potential for detection of *H. pylori* and can be an alternative to classical methods in diagnosis of the infection shortly. Studies targeting the development of similar new diagnostic methods are important since current methods are not sensitive and sufficiently specific, which negatively influences successful treatment.

Is the oral cavity a reservoir for *Helicobacter pylori*?

H. pylori has been observed in the saliva, tongue dorsum and dental plaques of patients. Thus, investigators have suggested that the oral cavity is a suitable place for the bacteria. Dental plaque is suggested to be a possible site of *H. pylori* with its ideal micro-aerophilic environment and glycoprotein matrix production for protection and reproduction of microbial population. Although the transmission of *H. pylori* through the oral cavity has been demonstrated in different studies, it has not been clearly identified whether it is a transient or permanent reservoir. Colonization of *H. pylori* in the oral cavity occurred due to vomiting. In a study by Vale and Vitor, bacterial DNA was identified in sub-gingival biofilms, saliva and dental plaques. These data suggest that these regions are potential reservoirs for *H. pylori*, however, the number of bacteria is not increased in the oral cavity after vomiting and it is lower than expected[19,75,76]. *H. pylori* is found in the oral cavity of almost 10% of patients with chronic gastritis. Therefore, it can be said that there is a significant relationship between chronic gastritis and *H. pylori* existence in dental plaques. This situation is a possible factor for the failure of eradication and reinfection. Poor oral hygiene is also an important factor for the recurrence of *H. pylori* infection. Hence, the use of a professional dental plaque remover is suggested throughout application of antibiotherapy for gastritis[77,78]. The presence of the small amount of *H. pylori* in the oral cavity causes difficulties in bacterial culture and false diagnosis of oral cavity infections[79]. The relationship between the presence of *H. pylori* in the oral cavity and periodontal status such as gingivitis or periodontitis has not been proven[80]. Some investigators[81] identified a relationship between *H. pylori*-colonized in the oral cavity and chronic gastritis and defined the oral cavity as a reservoir of the bacteria for gastric infections. DNA findings revealed the existence of *H. pylori* mostly in subgingival plaques (26.6%), supragingival plaques (20%) and saliva (10%) and an absence of bacteria in the tongue dorsum. Hence, these sites were identified as a bacteria reservoir of urease positive patients and also as a reservoir for reinfection[78,82,83]. However it is difficult to define a specific colonization site for *H. pylori* within the oral cavity. Bacteria are detected in all areas of the oral cavity, but data could not be compared to different methods were applied for detection[84]. In one study[85], *H. pylori* was positive in the samples obtained from the dental plaque of a child, while a second sample obtained two years later was negative for bacteria. This finding suggests that *H. pylori* is transiently present in the oral cavity.

More important than the transient or permanent existence of *H. pylori* in the oral cavity is whether oral *H. pylori* might lead to gastric *H.*

pylori. Numerous studies suggested a positive relationship between oral and gastric presence of *H. pylori*. However, different methods were applied in these studies for the detection of gastric infection and determination of oral *H. pylori*. Hence the sensitivities and specificities of these methods were variable[46,47,78].

At the present time, identification of different strains is possible by moleculer typing methods. The genome of *H. pylori* has significant variations; hence isolates obtained from different patients can be distinguished by varioius methods[86]. Determination of identical bacteria strains within the samples obtained from different sites of the human body or distinguished subjects may be a sign of transmission by investigated infectious agents. Therefore, recent findings that isolated bacteria from the oral cavity and stomach of individuals were identical was accepted by the researchers as significant since such data may support the role of oral cavity colonization in gastric *H. pylori* infection. For the first time in 1989, Shames et al[87] performed a RFLP analysis on samples isolated from the oral cavity and stomach of individuals to determine whether these *H. pylori* isolates is genetically similar. Investigators reported no difference between *H. pylori* isolated from dental plaque and the stomach of the same patient; however the strains were not the same when obtained from different patients. These results are further supported by the following studies[88-90]. However, in another study[91], PCR was applied to isolates obtained from three patients following DNA sequence analysis and *H. pylori* strains detected from the oral cavity were shown to be different from those obtained from stomach. In comparison, there are some other subjects that must be taken into account for determining similar strains of *H. pylori* in the stomach and oral cavity. It is known that one or more strains of *H. pylori* might be present in the stomach. Therefore, a *H. pylori* strain that is isolated from the oral cavity and is genetically identical to a gastric strain might not be from a gastric infection, although a distinguished strain may be the reason for the disease[92]. Moreover, oral colonization of the bacterium may stem from the translocation of *H. pylori* from the stomach to the oral cavity as a result of vomiting and gastric reflux. Nevertheless, the identification of the same strain in both the oral cavity and stomach suggests that the oral cavity might be a reservoir for gastric infection. Additionally, the role of oral colonization of *H. pylori* in the eradication of gastric infection is another important point that various studies have investigated. One study[93] demonstrated that following *H. pylori* eradication, almost 60% of the patients still have bacteria in the oral cavity. Two years later post-eradication, recurrence of gastric infection was also observed in approximately 30% of patients who had orally colonized *H. pylori*. According to these data, researchers thought that disease recurrence was directly associated with oral *H. pylori* and there was strong relationship between oral cavity and gastric infection[94]. Oral hygiene is thought to be another important factor for the fate of the infection. The recurrence rates of gastric infection were determined to be much higher for patients with poor oral hygiene. It was indicated that improving oral hygiene by using standard procedures led patients to give a more positive response to conventional antibiotic therapy[95,96]. Researchers also investigated whether having teeth or not influenced the presence of *H. pylori* in saliva. However, it was found that there was no relationship between natural teeth and *H. pylori* infection. A higher percentage of toothless patients were represented in the recurrence of the infection[97]. The interaction between oral *H. pylori* and halitosis was also examined by some researchers. *H. pylori* was detected in the saliva of only 16 of 102 individuals that had complaints of periodontitis and halitosis. Halitosis is a multifactorial entity including poor oral hygiene and systemic diseases. However, the study results showed that there was an indirect interaction between *H. pylori* infection and halitosis, and presence of bacteria in the oral cavity could be one of the reasons for halitosis[98]. There is also some data suggesting that *H. pylori* present in the oral cavity may not always be related to gastric infection. Some investigations demonstrated a commensal presence of the bacteria in the oral cavity. In other studies, the presence of *H. pylori* was shown to not cause any gastric disease in analyzed individuals and no anti *H. pylori* IgG antibodies were detected, proving the idea that there was an absence of any interaction between oral *H. pylori* and stomach colonization[86,99]. Reinfection is another crucial factor that threatens health. Some researches indicated that reinfection is more common in patients with uncontrolled dental plaques compared to patients with controlled plaques[100]. In gastritis, the oral cavity is not the only reservoir of bacteria. Bacteria may cause oral cavity erosions and it is suggested that it can be a significant factor for the development of aphthous ulcerations[98]. In some other studies, the dental plaques of patients who have chronic gastritis included a higher amount of *H. pylori* than their

stomach. This scenario was described as the oral cavity being the first area of colonization from where infection spreads to gastric mucosa[101]. As such, the literature indicates two different opinions about the main source of *H. pylori* infections. One group of researchers argues that there is a significant correlation between the presence of *H. pylori* within the oral cavity and gastric infection, while the other group defends the opposite. For the latter, *H. pylori* is considered as only an oral flora member and is not responsible for gastric infection. In this review, we choose all studies that reflect these two opposite opinions.

Studies demonstrating that the presence of *H. pylori* in the oral cavity is the cause of gastric infection

It has been suggested that dental plaque might harbor for *H. pylori*. There is some research reporting the mouth as a reservoir for *H. pylori* and as a possible source of reinfection to gastric mucosa. In 2009, researchers studied 101 patients with dyspepsia who had either periodontitis or not. Dental *H. pylori* was identified in the subgingival plaques of periodontal pockets. Then, *H. pylori* was evaluated by endoscopy and gastric antrum biopsies. More than 50% of the patients harbored the bacteria in the stomach, while *H. pylori* was positive in the dental plaques of 65% of patients. The percentage of *H. pylori* in dental plaque and the stomach was higher in patients with periodontitis than patients without periodontitis. In addition, *H. pylori* was detected in both the stomach and dental plaque of 78% of patients who had complaints of periodontitis, while in only 30% of the patients without periodontitis, where co-existence of the bacterium was observed in the two mentioned sites. In other words, the rates of existence of *H. pylori* in both the stomach and dental plaque are much higher for patients with poor oral hygiene in contrast to patients with good oral hygiene. Based on such data, researchers concluded that the oral cavity may act as a reservoir for *H. pylori,* and as a potential source of bacterial transmission to the stomach. They also suggested that the colonization of bacteria in the oral cavity and dental plaque might be a reason for reinfection[101]. In 2009, Silva et al[102] investigated the presence of *H. pylori* and its virulent cagA genes in the oral cavity of patients with *H. pylori* related-gastric diseases. The samples were analyzed by using specific primers for *H. pylori* 16S ribosomal and cagA genes, using a PCR-method. *H. pylori* was not present within saliva or dental plaques of the control group. Both oral and biopsy samples were *H. pylori* positive in 18 (60.0%) of the patients in the case group, and 8 (26.6%) of these patients had positive results for cagA-*H. pylori* DNA. The prevalence of *H. pylori* and its virulent clone was higher in the oral cavity of patients in the case group compared to controls ($p<0.05$). Their results revealed that in patients with gastric disease, saliva and dental plaques could serve as a temporary reservoir for *H. pylori* and its virulent cagA variant may be seen in bacteria that are localized in the oral cavity. In 2010, Eskandari et al[78] studied 67 patients with chronic periodontitis to detect *H. pylori* in dental plaques. In twenty-three of these patients, gastritis was diagnosed as well. Therefore, in this report, researchers investigated the presence of *H. pylori* in dental plaques of patients with chronic periodontitis with and without gastritis. To detect *H. pylori* in dental plaque specimens, a PCR-based method was applied. The results found *H. pylori* in 4 of 67 patients (5.97%). Interestingly, each of the patients whose dental plaque samples were positive for *H. pylori* had suffered from gastritis. In other words, 4 of 23 patients with gastritis had *H. pylori* in their dental plaques at a rate of 17.39%. The plaque specimens of the remaining 44 patients without gastritis were negative for *H. pylori*. As a result of this work, it was suggested that there was a significant relationship between gastritis and the presence of *H. pylori* in dental plaques ($p=0.012$). They concluded that dental plaques that are infected by *H. pylori* could be a source for recurrence of gastric infection, although it is rarely observed. In 2010, Rasmussen et al[103] studied 78 dyspeptic adults to investigate the relationship between oral *H. pylori* and gastritis. PCR and Southern blotting methods were used to determine the existence of *H. pylori* in stomach, saliva and dental plaque samples. In 14 of 76 patients (21%), every type of specimen (saliva, stomach and dental plaque) was positive for *H. pylori*. Furthermore, in 50% of patients with chronic gastritis, *H. pylori* DNA was detected either in dental plaque or saliva specimens, demonstrating a statistically meaningful interaction between the presence of *H. pylori* in the oral cavity and chronic gastritis. The authors proposed that the presence of a reservoir might result in recurrence of gastritis and reinfection based upon various distribution of the bacterium within the oral cavity.

Some researchers studied identification of helicobacterial virulence genes such as vacA and cagA in dental plaques and gastric mucosa of dyspeptic patients regarding similarity. One study was performed on 99 patients and as a result of PCR analysis, 95 patients were diagnosed as *H. pylori*-positive dependent on samples obtained from the stomach, while bacterial DNA was found in dental plaque specimens of 71 patients. For 63 of 71 patients (89%), *H.pylori* isolated from dental plaque and gastric mucosa consisted of identical vacA and cagA genotypes. Within six different genotypes, cagA positive- vacAs1bm1 was determined to be the most common as it was available both in dental plaque and stomach samples at a rate of 37%. The researchers concluded that simultaneous existence of these pathogenic strains in gastric mucosa and dental plaques was a sign of interaction between the presence of *H. pylori* in the oral cavity and gastric infection. However, it has to be noted that histological examination did not accurately confirm the results of the PCR assay in that study[104]. In a different paper[105], the researchers comprehensively examined whether root canals of endodontic-infected deciduous teeth might be a potential transmission source. The presence of the bacterium in dental plaques of endodontic-infected individuals was also examined. Various techniques such as 16S rRNA PCR, Western blotting, electron microscopy and culture method were applied on specimens obtained from root canals and dental plaques to detect live bacterium. Consequently, in 2 of 11 samples *H. pylori* isolated from the root canals was successfully cultivated and the presence of the bacterium was confirmed by Western blotting and urease assay. There was no growth of *H. pylori* in the samples obtained from dental plaques. PCR analysis did not give accurate results for both dental plaque and root canal samples. According to this data, the root canals of teeth were accepted as a reservoir for *H. pylori* by the authors and it was also proposed that it might be a possible transmission source for gastric *H. pylori* infection. In 2012, Momtaz et al[106] worked with 300 antral gastric biopsies, dental plaque, stool and saliva samples to compare the genotypes of *H. pylori* that were isolated from these samples to evaluate the transmission mode of *H. pylori* infection. The presence of the bacterium in every specimen was detected by PCR assay and Rapid Urease Test (RUT). Based on RUT analysis, 271 patients (90.33%) were found to be positive for *H. pylori*, while gastric specimens of 233 patients were positive according to PCR assay. Meanwhile, in saliva samples of 25 patients, *H. pylori* was detected, while 167 of stool samples were found to be positive for the bacterium. Notably, *H. pylori* was not detected in any of the dental plaque specimens. Identification of virulence genes of *H. pylori* was also carried out PCR and various vacA genotypes were determined. The frequencies of cagA gene were evaluated as 94, 42, 100 and 97% for gastric biopsy, saliva and stool samples, respectively. Furthermore, the most common variants of vacA gene were s1a/m2 as it was seen in 72, 71, 85 and 25.75% of *H. pylori* positive saliva, stool and biopsy samples, respectively. However, there was no correlation between the genotypes of the isolate from saliva and gastric biopsy as vacaA genotypes of bacteria in saliva and biopsy samples of same patient demonstrated diversity. The authors note that the fecal-oral route is an important method of *H. pylori* transmission since there was a high similarity between bacterium strains that were obtained from the saliva and stool specimens of an individual. On the other hand, the genotypic variations between virulence factors of *H. pylori* strain isolated from saliva and gastric biopsy led researchers to think that the same patient could have more than one *H. pylori* genotype. In a different study[107], researchers looked at the interaction between dental plaque control and gastric *H. pylori* based infection. The study included 107 individuals, 56 of whom received dental plaque control. The presence of the bacterium was evaluated by 13 C-Urea Breath Test that was applied to all patients. The prevalence of *H. pylori* was determined to be significantly higher for patients without controlled dental plaques (84.3%) in contrast to those who received dental plaque control (19.6%). The authors suggested that the health of dental plaques may play an important role in gastric infection or prevention of re-infection. Based on this data, it is possible that the risk of harboring gastric helicobacterial infection is remarkably lower for individuals with well-managed dental plaque health. In another study[108], researchers performed a meta-analysis to find the correlation between the presence of the bacterium in the oral cavity and gastric infection. Bacterium presence was detected in 45% of patients whose gastric biopsy samples were positive for *H. pylori*. In comparison, only 23.9% of patients whose biopsy samples were negative for *H. pylori*, were orally infected by the bacterium. Additionally, 44.8% of patients who had previous

gastroesophageal disease had oral cavity samples that were positive for *H. pylori*. Meanwhile, this rate decreased sharply to 13.2% in patients without gastric disease. Additionally, the authors determined that eradication rates of *H. pylori* were dramatically changed according to the place where the bacterium was found. The eradication rate was 85.8% when bacterium was found in the stomach, while it was only 5.7% when the bacterium was localized in the oral cavity. Consequently, it was strongly suggested that the oral cavity could be a potential source of reinfection due to difficulty of bacteria eradication in the oral cavity. Furthermore, it was finally concluded that there was substantive interaction between gastric infection and the existence of the bacterium within the oral cavity[108]. In 2014, Wang et al[109] investigated the relationship between orally-present *H. pylori* and successful treatment of gastric infection induced by *H. pylori*. At the end of the study, the authors found that treatment of orally colonized *H. pylori* with mouthwash solutions increased the success of eradication of *H. pylori* within the stomach that was treated with classical drug eradication therapy. The results showed that oral hygiene is an important factor for gastric *H. pylori* infection since cleaning of the mouth with an antibacterial solution gave rise to an increase in eradication rates using classical drug therapy. The authors proposed that there was a meaningful relationship between orally colonized *H. pylori* and gastric infection.

Studies demonstrating that the presence of *H. pylori* in the oral cavity is not responsible for gastric infection

Although a great majority of the research investigating the relationship between dental plaque and *H. pylori* infections suggest that dental plaque can be an alternative reservoir for this bacterium to infect gastric mucosa, some studies assert the contrary. Researchers who support this opposite opinion suggest that *H. pylori* found in the oral cavity is not responsible for the infection of gastric mucosa and therefore *H. pylori* can be a member of normal oral microflora. In all of these studies, researchers detected the presence of *H. pylori* in dental plaque and the oral cavity by using different diagnostic techniques and all of them indicated that no bacterium existed in specimens taken from the oral cavity and dental plaques of individuals.

In an early work published by Hardo et al[110] in 1995, 62 patients with dyspeptic symptoms were investigated for oral hygiene and periodontal disease before endoscopy. The existence of *H. pylori* in the dental plaque was checked using VCAT culture and the PCR technique, which is specific to the 16S ribosomal RNA of the bacterium, and histological examination including embedding in paraffin and staining with hematoxylin-eosin was applied on gastric biopsy specimens. *H. pylori* was detected in the biopsy specimen of 34 patients (54%). Interestingly, culture of samples obtained from the plaques gave negative results for *H. pylori*. Furthermore, only one patient's specimen was positive with PCR. *H. pylori* gastritis did not reveal any correlation with either periodontal disease or dental hygiene. These results suggest that dentures and dental plaques do not play a significant role in the transmission of the organism and are not important reservoirs for *H. pylori*. The authors explained one positive PCR result by the probability of contamination during sample collection from the denture. They also suggested that conflicting results in published work related to the presence of *H. pylori* in the oral cavity could arise from different sample collection and cultivation techniques or contamination of the oral environment with gastric juice due to gastro-esophageal reflux during endoscopy. In 2000, Song et al[99] compared the presence of *H. pylori* in samples obtained from different regions of the oral cavity such as molar, premolar, incisors and saliva and in samples taken from the stomach of 42 patients. Biopsy specimens were analyzed by a ^{13}C-Urea Breath Test. PCR was used on oral specimens. In their results, only 26.2% of the patients (n=11) were determined as *H. pylori* positive when their stomach samples were investigated. However, *H. pylori* was detected in the dental plaque samples of 41 patients (97%). Moreover, in saliva samples of 23 patients (55%), the bacterium was detected by PCR. These outcomes demonstrated that there is a characteristic distribution of *H. pylori* in the oral cavity independent from gastric infection. Therefore, it was pointed out that *H. pylori* could be a member of normal microflora of the oral cavity. In 2002, Goosen et al[111] developed a novel heminested PCR protocol in order to detect *H. pylori*. They used a set of primers specific for the *H. pylori* phosphoglucosamine mutase gene (glmM) which produces a 765-bp fragment. In this protocol, only 0,1 pg genomic DNA of *H. pylori*, which is equivalent to 5 x10^2 bacteria was

sufficient for the detection of bacterium. The study was performed on specimens obtained from saliva and dental plaques of 58 individuals in South Africa. After collection, specimens were cultivated and the PCR protocol was applied to bacterial colonies that were grown from oral specimens. In 8 of 58 oral samples which were inoculated into brain heart infusion agar, *H. pylori*-like colonies were visualized. After purification of colonies from the medium, some biochemical tests including production of urease and catalase and microaerophilic growth were performed. From this 8-sample group, five isolates were negative in PCR assays and were considered to be non-*Helicobacter* spp. By PCR, just three samples (two saliva and one dental plaque) had the 933-bp amplification product, using HPU50 and HPU25 primers. However, only two of these samples were positive by heminested PCR. One of these two saliva samples which was positive with HPU50-HPU25 PCR was shown to be negative by heminested PCR assay. In all situations, positive controls were always positive and negative controls were always negative when PCR was applied. Thus, this excludes the probability of contamination. As a result, the prevalence of *H. pylori* was as low as almost 3% in oral cavity specimens, which suggests that the oral cavity is not an appropriate site for colonization of *H. pylori*. The authors suggested that the reason for low detection rates of *H. pylori* was due to difficulties in culturing viable, but coccoidal *H. pylori* bacterium in saliva. In 2004, Czesnikiewıcz-guzik et al[96] determined gastric *H. pylori* infection by UBT and monitored the presence of bacteria in the oral cavity from the dental plaque and by the culture from the saliva in their study. Gastric *H. pylori* was identified in 51% of the study patients and oral *H. pylori* was present in 54% of saliva and 48.3% of gingival pockets. They concluded that contamination of the oral cavity with *H. pylori* was present at similar degrees as the stomach and that the oral cavity had only transient food-related contamination without giving rise to gastric infection. In 2005, Olivier et al[112] conducted a study on 79 healthy individuals who had high seroprevalence for *H. pylori* infection. The existence of bacterium in samples isolated from the oral cavity and gastric biopsies was detected by PCR and microscopic (hematoxylin-eosin stain) techniques. In the dental plaque and biopsy samples, they applied heminested PCR which is directed toward the phosphoglucosamine mutase (glmM) gene and a single-step PCR directed toward the urease AB gene of *H. pylori*. A third nested PCR was applied on dental plaque samples which was directed toward the 860-bp DNA region of *H. pylori*. The histology results showed that 84% of the individuals were positive for *H. pylori* infection, which confirmed the reported high prevalence of infection in this community. Amplification of the urease AB gene was not present in any of the dental plaque samples, while amplification was observed in all the dental plaque samples, which spiked with the positive control. In 2005, Czesnikiewicz-Guzik et al[113] performed a work in order to determine the effectiveness of oral *H. pylori* on gastric infection and release of the gut ghrelin hormone, which stimulates starvation and gastric secretion in the stomach. In this study, again the prevalence of gastric and oral *H. pylori* was compared. *H. pylori* existence in the stomach was evaluated by a 13C-Urea Breath Test, and was assessed by a culture method for the oral cavity. The levels of anti *H. pylori* IgG, anti-cagA, anti- VacA, gastrin, ghrelin, IL-8 in blood serum and levels of anti-*H. pylori* IgA in saliva was determined by ELISA test. Results of the study demonstrated that *H. pylori* existed in the oral cavity of 54% of 100 patients. This rate was 51% for gastric infection. However, no correlation was shown between gastric infection and the presence of bacteria in the oral cavity, since 45.1% of patients who were considered positive by UBT for gastric infection demonstrated no *H. pylori* existence in saliva while 43.1% of this group did not have *H. pylori* in supragingival plaque. In contrast, 53.2% of patients who did not show gastric infection had *H. pylori* in their saliva and 42.9% of these non-infected individuals demonstrated the presence of *H. pylori* bacterium in their supragingival plaques. Moreover, the presence or absence of *H. pylori* in the oral cavity did not result in any remarkable change in serum levels of ghrelin and gastrin. However, in patients with gastric infection, ghrelin levels in serum significantly decreased, while gastrin levels were increased when compared to patients without gastric infection. All of these results were rendered by authors to argue that the presence of *H. pylori* in the oral cavity was not a sign of gastric infection, and that oral *H. pylori* could not change the levels of hormones that are responsible for appetite sense, which is a signature of gastric *H. pylori* infection. In 2006, Chitsazi et al[114] investigated the diagnostic value of dental plaque for gastric *H. pylori* infections. For this aim, gastric biopsy specimens

of 88 patients with symptoms of dyspepsia were analyzed by a Rapid Urease Test (RUT) for bacterium existence and it was observed that only 44 patients had gastric infection. Following this examination, oral specimens were taken from dental plaques of both *H. pylori*-infected and non *H. pylori* infected patients for comparison. The prevalence of *H. pylori* infection in dental plaque was demonstrated to be 31.8% *vs.* 36.4% in patients with and without gastric infection, respectively. This result indicates that there is no relationship between the presence of gastric infection and presence of bacteria in dental plaque. The authors suggested that *H. pylori* might be a member of normal flora in the oral cavity and therefore its presence in dental plaque had no diagnostic value. This study also compared the prevalence of the bacterium in the stomach and dental plaques of male and female individuals. *H. pylori* prevalence was higher in male patients than females indicating that males are more susceptible of *H. pylori* infections. In 2009, Rossi-Aguiar et al[115] conducted another study on 43 patients in Brazil complaining of epigastric pain. The presence of gastric *H. pylori* infection was analyzed using a urea-breath test or a rapid urease test. Samples taken from saliva, supragingival dental plaques and tongue dorsum were tested for *H. pylori* existence with PCR, using primers targeting cagA and vacA genes. Thirty patients were determined to be positive regarding gastric infection. However, no bacterium was detected in oral samples. These results again demonstrated that in patients with epigastric pain, the oral cavity may not be a reservoir for *H. pylori* as the bacterium was detected only in the stomach. In 2012, Al Ahmad et al[116] also investigated the interaction between the presence of *H. pylori* within the oral cavity and gastric infection. They conducted the study on 15 patients whose gastric biopsy specimens were found to be positive for *H. pylori*. In total, 163 samples were obtained from different regions of the oral cavities of patients, such as supragingival and subgingival plaque, saliva, periapical exudates and tongue swabs and all samples were examined with PCR by using two different primers that were specific for *H. pylori*. *H. pylori* was not detected in any of the samples that were taken from 14 patients. The authors observed positive signals in regards to *H. pylori* existence in only in two samples of one patient. However, this result was obtained from only one primer, and *H. pylori* could not be detected by using the second primer. Additionally, cultivation of *H. pylori* was not achieved before transfer of each of two PCR-positive samples into selective medium. Therefore, the researchers could not find any correlation between orally colonized *H. pylori* and gastric infection. The researchers proposed that *H. pylori* must be considered as transiently-colonized bacterium within the oral cavity. In 2012, Sepulveda et al[117] performed a study in order to compare the virulence genes of *H. pylori* bacterium that were isolated from stomachs and oral cavities of 18 patients. vacA and cagA genes were selected for this study since they were known as the most important virulence factors of the bacterium. *H. pylori* existence was investigated by applying PCR and RT-PCR on all samples. In the results, seven different cagA and vacA m1 genotype combinations were detected and all combinations were found to vary for isolates taken from gastric biopsies and the oral cavities of patients. For these results, the researchers could not find a significant relation between oral *H. pylori* and gastric infection. In conclusion, there are still contradictions in the research literature about what is the main reservoir of gastric *H. pylori* infection. It is thought that this inability to determine the main reservoir of infection may also result in false treatment applications. New treatment regimens, as mentioned below, involve triple therapy that also consists of acid suppressors and stomach protectors, in addition to antibiotics, and target only the bacterial infection in the gastric system. Thus, the eradication of bacteria residing in extra-gastric reservoirs are missed. Hence, clarification of the main reservoir of *H. pylori* is of substantial interest for the aim of total eradication of the infection and complete prevention of re-infections.

Treatment

Despite ongoing studies to develop effective treatments against *H. pylori* infection, there is as yet no optimal therapy regimen. Antibiotics such as metronidazole, clarithromycin, tetracycline and amoxicillin are usually applied for treatment of *H. pylori* infection. However, administration of a single antibiotic frequently does not provide eradication of *H. pylori*-related diseases. The most important reason for failures in *H. pylori* therapy is the rapid growth of resistance against metronidazole and clarithromycin[118-120]. According to recent reports, the prevalence rates of clarithromycin resistance in patients infected with *H.*

pylori has reached 20% in Europe, 12% in the USA, 13% in Japan and 4.5% in China. Metronidazole resistance is more widely seen worldwide in comparison to clarithromycin resistance. It is estimated that prevalence rates of metronidazole resistance range between 15% and 40% in Europe and the USA. In some developing countries, metronidazole resistance rates were found to reach 80%[121,122]. Hence, the success of treatment with a single antibiotic has decreased to unacceptable levels worldwide. In order to overcome resistance against metronidazole, clinicians apply high dosages of this drug and partially succeed. However, resistance to clarithromycin, which is the most widely applied drug against *H. pylori*, cannot be overcome with application of high doses[123]. Therefore, multiple antibiotic applications come into use in order to enhance the efficacies of treatment. Triple therapy, which means administration of a combination approach, includes antibiotics, antimicrobials and drugs that increase gastric pH for 7-10 days. This is now the most frequently used treatment option for eradication of *H. pylori* infection. In this therapy, antibiotics such as clarithromycin, metronidazole, or amoxicillin are applied in conjunction with proton pump inhibitors (PPI) such as lansoprazole, omeprazole, pantoprazole, rabeprazole, dexlansoprazole, and esomeprazole[124,125]. Triple therapy including PPI, clarithromycin (500 mg/12 h) and amoxicillin (1 g/12 h) is accepted as a first line treatment option in areas where there is low clarithromycin resistance. The duration of this therapy is unclear. Some clinicians perform triple therapy for 7 days, some for 14 days. It was demonstrated that 14 d treatment generated a 5% higher eradication rate in contrast to 7d triple therapy. If the patient has allergy to penicillin group antibiotics, amoxicillin can be substituted with metronidazole, which shows equivalent effectiveness against *H. pylori*[126,127]. Triple therapy applications may provide successful treatment of *H. pylori* at rates reaching 96%. However, recent reports indicate that eradication rates following triple therapy have decreased to 70-85% in different regions of the world due to enhanced clarithromycin resistance[128,129]. Meanwhile, it is predicted that eradication rates following triple therapy is more successful when *H. pylori* is absent in the oral cavity. Eradication rate decreases to 52% when the microorganism is present orally. This suggests that extra-gastric reservoirs of *H. pylori* can lead to re-infection of the disease. Therefore, extra-gastric reservoirs of *H. pylori* must also be taken into consideration in the development of new treatment approaches to eradicate the infection[130-132]. Clinicians apply quadruple therapy in the areas where clarithromycin resistance is high. In that situation, a combination of a proton pump inhibitors, bismuth sub-salicylate (525 mg, × 4 daily), and two different antibiotics, frequently metronidazole (250 mg × 4 daily) and tetracycline (500 mg, × 4 daily) are administered to patients for 10 or 14 days. Clinicians obtained good results on recruitment of *H. pylori* infection with quadruple therapy. In various studies, bismuth containing quadruple therapy was more effective than standard triple therapy for eradication of *H. pylori*[133].

This treatment regimen, however, has some disadvantages such as complexity of administration and adverse side effects that restricts use to in clinic. Furthermore, recent papers showed that quadruple therapy resulted in failures to eradicate *H. pylori* infection in 20-30% of all cases. Moreover, the unavailability of tetracycline in several countries is another problem that prevents the application of quadruple therapy[133-135]. Levofloxacin, which is included in a triple-therapy regimen, is another second-line treatment option for eradication of *H. pylori* infection. In this treatment approach levofloxacin is administered to patients for ten days in combination with amoxicilin and a proton pump inhibitor[136,137]. In researches performed in Italy and Spain, levofloxacin-containing triple therapy was demonstrated to reach success at rates of at most 80%[138-140]. However, these eradication rates cannot be accepted as optimal in treatment of *H. pylori* according to present treatment success grading system levels. It is reported that a treatment approach has to reach eradication rates of at least 90% in order to be considered as an ideal anti-*H. pylori* treatment regimen. Therefore, levofloxacin-containing triple therapy is far from being an ideal therapy option for eradication of *H. pylori*[141]. Because of all these reasons, researchers continue to search for new alternative treatment approaches to conventional antibiotic applications in order to cope with these resistance problems. Probiotics are another alternative therapeutic option in the treatment of *H. pylori* infection. Probiotics are an oral supplement or food products that contain viable microorganisms that may alter the host microbiota and has the potential to produce beneficial effects[142,143]. Probiotic microorganisms are commonly classified in the *Bi-*

fidobacterium, Lactobacillus and *Streptococcus* family[144,145]. Moreover, some spore producing bacteria such as *Bacillus clausii* are widely used in probiotic based treatment of *H. Pylori* infections in different regions of the world[146]. Similarly, some yeast including *Saccharomyces boulardii* and their byproducts, have also been applied as probiotic agents. Antagonistic properties of several probiotic strains (particularly lactobacilli) against *H. pylori* have been shown *in vivo*[147]. Several effect mechanisms of probiotic efficacy have been suggested. Gastroduodenal microbiota including *Lactobacilli* can generate a strong defense against harmful microorganisms[148]. Hence, exogenous intake of the lactic acid bacteria could strengthen protective facilities within the gastro-intestinal system by directly attacking *H. pylori* and diminishing inflammation[147]. Gastric acidity and gastric mucosal barriers are also first-line defense mechanisms against pathogenic bacteria[149]. Probiotics decrease gastric pH by producing short-chain fatty acids (SCFAs) including butyric, propionic, acetic and lactic acids that inhibit *H. pylori.* Lactic acid can also inhibit urease enzymes of *H. pylori*. Some lactobacilli may synthesize bacteriocin compounds that have anti-*H. pylori* activity[149]. Probiotics may also inhibit the adhesion properties of *H. pylori* to epithelial cells. The adhesion preventing activity of certain lactobacilli are exerted by competing with adhesion molecules or by secreting antimicrobial substances[150,151]. One of the major symptoms for *H. pylori*-related gastritis is a decrease in mucus secretion in damaged gastric epithelium. Probiotics may strengthen the mucosal barrier by stimulating mucin production through enhanced expression of MUC2 and MUC3 genes, *in vitro*[152]. Another anti-*H. pylori* activity of probiotics is due to modulation of the immune response to pathogens through the release of many inflammatory mediators, such as cytokines and chemokines[150]. Probiotics may alter the host immune-response by activating epithelial cells and regulating the secretion of anti-inflammatory cytokines in order to reduce inflammation and gastric action[153]. Some investigators studied the effectiveness of probiotics as a single therapy in the eradication of *H. pylori* infection in both adults and children. Culture supernatants that were derived from probiotic strains are shown to suppress *H. pylori* growth *in vitro* and *in vivo*; however, eradication could not be obtained without applying antibiotics and a proton pump inhibitor[154]. In a study by Gotteland et al[155], eradication of *H. pylori* was achieved in 12% of children exposed to *Saccharomyces boulardii* and 7% of children exposed to *Lactobacillus acidophilus* for 8 weeks, while two-thirds of children were treated with standard triple therapy. Researchers suggested that probiotics undertake complementary roles to conventional *H. pylori* therapy by reducing side effects, enhancing tolerability and ameliorating compliance. However, the beneficial role of this strategy in increasing the eradication rate is confusing. In a prospective study by De Bertoli et al[156], co-administration of bovine-acquired inulin and lactoferrin with nine different probiotics enhanced the eradication rate of conventional triple therapy from 72% to 89%. A reasonable amount of evidence suggests that supplementation of triple therapy with *S. boulardii* is useful in eradicating *H. pylori*[157]. In a study by Song et al[158], 4-week administration of *S. boulardii* together with classical triple therapy for one week augmented the rates of H. pylori eradication by 10%. Another study[159] has shown that co-administration of *S. boulardii* not only enhanced the rate of eradication, but also decreased the adverse effects related to *H. pylori* therapy, particularly diarrhea. The effect of probiotics other then *S. boulardii* are not so clearly established. In a study by da Silva et al[160], the administration of *Lactobacillus acidophilus* did not significantly increase eradication rates in patients with complaints of peptic ulcer treated with conventional triple therapy whose strains are susceptible to both antibiotics. In another study[161], conventional triple therapy enriched with Bifidobacterium containing yogurt did not achieve any enhancement in eradication rates; however, there was decreased digestive side effects such as stomatitis and constipation. In a systematic review by Jinda et al[162], it was demonstrated that probiotics were efficient as a complementary therapy to decrease the side effects of standard *H. pylori* eradication treatment. In conclusion, probiotics do not influence the fate of *H. pylori* infection as a single agent. However, there is increasing evidence to support their role as an adjunctive therapy that can enhance the eradication rate of the bacterium and decrease the redundancy and severity of side effects that arise from applications of antimicrobial agents in conventional combination therapies. Consequently, more comprehensive studies are further required to identify which strain, dose and administration route of the probiotics should be applied to demonstrate benefit in the management of *H. pylori* infection.

Vaccination

H. pylori eradication is applied only to patients with symptoms. Treatment includes the combination of a proton pump inhibitor and two different antibiotics. This regimen is applied daily for approximately one or two weeks[141]. Although eradication is achieved in almost 80% of the cases, drug treatment results in problems such as side effects and decreased patient compliance according to the high number of tablets consumed every day. Progressively increasing antibiotic resistant strains and high reinfection rates in high transmission areas are additional problems in *H. pylori* treatment. Moreover, treatment of only symptomatic patients leaves asymptomatic patients at risk of severe complications such as gastric cancer and atrophic gastritis[163,164]. In order to overcome these problems, various investigations have been done with different approaches to developing prophylactic and/or therapeutic vaccines for *H. pylori*. Nevertheless, the development of a therapeutic or preventive vaccine against *H. pylori* is still elusive. Commonly, antigens are chosen as potential vaccine candidates. An ideal vaccine candidate should be highly immunogenic and well-conserved in all strains of one bacterium in order to stimulate an extensive and strong immune response[162]. Thus, the urease antigen is a potential vaccine candidate against *H. pylori*. Therefore, the first attempts for vaccine development were primarily focused on using recombinant urease as the antigen[165]. Although, the results on animal studies were promising, human studies were hampered because of the gastrointestinal side effects caused mainly by the mucosal adjuvant. In a recent study, investigators developed a trivalent vaccine containing recombinant VacA, CagA and neutrophil activating protein administrated by intramuscular route[166,167]. Despite the recognition of these antigens by the humoral and cellular immune systems of the hosts, immunity was not observed in a challenge model. Some studies addressed novel antigens and adjuvants, however, all of them were small animal studies and comprehensive vaccine studies have to be performed on humans in the near future. Using new formulations containing multiple antigens and applying various methods in order to mediate cellular immunity may lead to improvement in the effectiveness of vaccine candidates. To improve efficacy, vaccine formulations should include multiple antigens and methods should be developed to optimize cellular immunity[168]. In such an approach, Chen et al[169] prepared two different mixtures of *H. pylori* oipA gene encoded plasmid with B subunit heat labeled toxin of *E. coli* gene encoded plasmid and IL-2 gene encoded plasmid and they investigated the effectivenesses of these formulations in mice after *H. pylori* challenge. Co-delivery of these immunogenic molecules by intradermal route shifted the immune response from Th1 to Th2 biased and resulted in greater clearance of bacteria after *H. pylori* challenge. In another study, DeLyria et al[170] used *H. pylori* lysates that were prepared by sonication as antigen and cholera toxin as adjuvant on IL-17A and IL-17A receptor knock out mice. Interestingly, the protective immune response in IL-17A and IL-17A receptor knock out mice against *H. pylori* or *H. felis* did not vary following application of the formulations and bacterial challenge in contrast to wild type mice. This was contrary to previous reports that demonstrated that IL-17 antibody contributed to the immune response against *H. pylori* by regulating the neutralization process during challenge of mice with bacterium[171]. The main issue that complicates the development of an effective vaccine against helicobacterial infections is the inability to produce an effective antibody response. *H. pylori* is shown to have extensive mechanisms to evade the immune responses of the host and current vaccine strategies have failed to produce sterilizing immunity in animal models and clinical studies have failed to demonstrate vaccine efficacy. Another issue is the challenge of enlisting large pharmaceutical companies to invest the large amount of money required for future research in light of the long list of failed preclinical and clinical studies, with the development of a vaccine for clinical use being a long and expensive process. To develop a successful vaccine against *H. pylori*, it should be therapeutic rather than prophylactic. Prophylactic vaccines should be administered to individuals very early in childhood, preferably before two years of age. However, at this age group, children are vaccinated against several diseases and this can prevent the production of sufficient immune responses against helicobacterial infection. Moreover, since half of the worlds' population is predicted to be infected with *H. pylori*, prophylactic vaccines may not be as effective as desired. Therefore, the development of a therapeutic vaccine is considered as a better option. This type of vaccine can be applied to not only children, but also individuals at each age group. Furthermore, these vaccines can be administered to people who are already infected with *H. pylori*. However, it is known that coping with an established *H. pylori* infection is

not easy, since the bacteria have an ability to overwhelm host immune responses[172,173]. Nevertheless, human studies of prophylactic and therapeutic vaccine candidates are currently ongoing. Further investigations will hopefully answer fundamental questions regarding host-microbe interactions and in the future there may be new vaccines that are effective against *H. pylori* infections and lead to eradication of this pathogen.

Future Prospects

As mentioned, problems related to *H. pylori* infection continue to exist and infection is globally threatening the lives of millions of people. This situation continues even though there has been considerable research done in regards to the biology of infections, host-infection relations, epidemiology, diagnosis, treatment and vaccination. Additionally, there continues to be contradictory evidence about extra-gastric reservoirs for the bacterium, such as in dental plaque or the oral cavity. Determining such sources is another important factor that may be important for prevention and eradication of the disease. Based on literature analysis, we put forward several new approaches as detailed as below. These approaches may facilitate further studies aimed at fighting the infection and decreasing its distribution worldwide.

The current use of various diagnostic methods reveals the lack of a gold standard *H. pylori* detection technique. It is necessary to develop new diagnostic methods that provide accurate and rapid detection of bacterial presence in samples. In our recent study, we showed that the Micro Culture Method (MCM), which is intensively applied in order to detect micro-aerophilic protozoons such as *Leishmania* parasites, could be an alternative diagnostic method for detecting micro-aerophilic *H. pylori*, since it exhibited 96% sensitivity. In our previous study, we showed for first time that MCM possessed approximately 96% sensitivity in detecting *H. pylori* presence in biopsy specimens, compared to the 54% sensitivity with the classical culture method. Thus, MCM has tremendous potential for addressing the disadvantages of common diagnostic methods that are currently used to detect *H. pylori* infection. As such, studies should continue along this line.

Similarly, the development of diagnostic kits based on monoclonal antibodies via hybridoma technology may be another alternative to current diagnosis tools. *H. pylori* consists of several antigenic molecules that play predominant active roles in its virulence and pathogenicity. Isolation of antigens alone or as mixtures from whole bacterium and production of monoclonal antibodies against these antigens could facilitate the design of new diagnostic methods that demonstrate high sensitivity and specifity.

For treatment of *H. pylori* infection, past research has mainly focused on the development of new antimicrobials that have a capacity to eradicate *H. Pylori*. Due to drug resistance problems, this may not be an optimal approach. The use of micro/nanoparticulate drug delivery systems is one contemporary track. In several studies, delivery systems composed from micro/nanoparticulate polymers have been designed to transport conventional anti-helicobacterial drugs more effectively and strongly into infection sites and have had promising results. Shortly, therapy regimens based on delivery systems may be applied in clinic.

The lack of an effective and protective vaccine is also an important reason for the wide distribution of *H. pylori* infection all over the world. New vaccine formulations with characteristics of both therapy and prophylaxis are promising candidates for the prevention of the diseases bound to *H. pylori*. Moreover, in recent years, use of vaccine delivery systems, especially those based on natural or synthetic polymers have gained importance for protection against some infectious diseases. These antigen delivery systems frequently demonstrate adjuvant properties and can sufficiently induce antigen presenting cells (APCs). This may lead to a stronger immune response against the infection. Further knowledge and improvements in polymeric delivery systems may be adapted to research targeting the development of strong anti-helicobacterial vaccine candidates.

Furthermore, our literature analysis exhibited the presence of *H. pylori* in the oral cavity of some individuals. This was proven by several studies indicating the presence of the bacterium in oral samples of either patients or volunteers with different diagnostic methods. However, precise correlation between gastric infection and orally colonized *H. pylori* continues to be inconclusive. Unfortunately, studies exploring this interaction remain insufficient. We think that more research must be done to address and provide an answer about the relation between gastric infection and localization of the bacteria. If the correlation between orally colonized *H. pylori* and gastric infection is accurately proven, this would be very important for alteration of eradication techniques in treatment of

H. pylori infection. In addition, the lack of a gold standard diagnostic method may be a major factor limiting the determination of defintive results about extra-gastric reservoirs of the bacterium. We think that the development of new, rapid and more sensitive diagnostic methods would facilitate the determination of different reservoirs of *H. pylori*, apart from the gastric system, and could lead to changes to conventional treatment methods.

Host-bacterium interaction is also an important factor in invasion of the disease. Several molecules at the surface or inside of the bacterium have active roles in pathogenicity. Although the chemical compositions of these molecules have been identified, their mode of actions in exerting the disease is still unclear. It is known that *H. pylori* infection influences different metabolic pathways by either stimulating or inactivating their mechanisms. In developing new antimicrobial substances, the investigation of host-bacterium interactions, upregulated or down-regulated pathways and chemical structures of virulence factors are very important. Hence, we think that improving knowledge about the action mechanisms of helicobacterial virulence factors inside the host will facilitate the development of new substances to prevent or mitigate invasion tracks by the infection inside host cells.

Probiotics are oral supplements or food products that contain viable microorganisms that may alter host microbiota and may produce beneficial effects. Probiotics are an alternative therapeutic option in the treatment of *H. pylori*. Currently, probiotics cannot be applied as a single therapy in the treatment of *H. pylori* infections, however, there is increasing evidence to support their role as an adjunctive therapy. Probiotics might enhance the eradication rate of the pathogen and reduce the adverse effects of standard triple therapy. Standardized, multi-center, placebo-controlled studies with larger series are required to identify the best strain, dose and administration route to be applied when using probiotics for the management of *H. pylori* infections.

Conclusions

As known, *H. pylori* infection is one of the most important and serious infectious diseases in the world today. It continues to spread worldwide day by day. According to the most recent data, half of the world's population is predicted to be infected with *H. pylori*. There is strong evidence that *H. pylori* infection is associated with gastric MALT lymphoma. Although, the mortality rates of *H. pylori* related-MALT lymphoma have not been definitely described, in the USA alone there are 70,000 new MALT lymphoma cases diagnosed each year. Considering the high incidence rates of MALT lymphoma and strong relationship between *H. pylori* infection and cancer, the eradication of *H. pylori* infection is very important for decreasing the number of stomach cancer cases and preventing rapid distribution of the disease. Currently, there are many challenges to eradication of the disease. The major challenges include the lack of a gold standard diagnostic method, lack of an effective-protective vaccine, evolved resistance in bacteria against current drugs, and failure of conventional treatment applications. In this review, we closely reviewed the role of bacterium reservoirs, apart from that in the gastro-intestinal tract, and implications on the effectiveness of treatment procedures. Until now, current therapies have mainly targeted the bacterium residing in epithelial cells within the stomach. However, the existence of bacterium in dental plaque and oral cavity has been continously ignored. Despite contradictions about the role of the oral cavity on gastric infection, in recent studies researchers have frequently defended that oral derived *H. pylori* is responsible for gastric infection. We expect that in a five-year period going forward, we will see research that confirms the oral cavity and dental plaque as extra-gastric reservoirs of *H. pylori* infections in the stomach. Furthermore, we think that treatment regimens may be changed in order to target microorganisms residing not only in the stomach, but also in the oral cavity.

Conflict of Interest

The authors declare that they have no conflict of interests.

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